(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 02/057228 A1

(51) International Patent Classification[7]: C07D 207/34, A61K 31/40, A61P 3/06

(21) International Application Number: PCT/IN01/00004

(22) International Filing Date: 17 January 2001 (17.01.2001)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PC25686A
APP. NO. 10/828,398 FILED: 04/20/2004

WO 02/057228 A1

(54) Title: ATORVASTATIN CALCIUM

(57) Abstract: A process for the preparation of amorphous atorvastatin calcium and its hydrates thereof which comprises: (a) dissolving heterogeneous mixture of atorvastatin calcium in a non-hydroxylic solvent; (b) adding a non-hydroxylic solvent or adding the dissolved atorvastatin to the non-hydroxylic solvent to precipitate out atorvastatin calcium; and (c) removing the solvent by filtration to afford amorphous atorvastatin calcium.

ATORVASTATIN CALCIUM

FIELD OF THE INVENTION

The present invention relates to a process for the production of amorphous atorvastatin calcium.

BACKGROUND OF THE INVENTION

The process for the production of amorphous [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt.

Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease.

United States Patent 5,273,995, describes that R-form of the ring opened acid form inhibits the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. amorphous [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-

3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (2: 1) is discussed in literature.

Various United States patents like, 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,248.793; 5,280.126; 5,342,952, which are herein incorporated by reference, describe various processes and key intermediates for preparing atorvastatin calcium.

The process mentioned in the above patents does not produce atorvastatin calcium in its amorphous form consistently. Often a mixture of crystalline and amorphous form is obtained which is not suitable for filtration and drying and therefore not a desirable process for large-scale production.

PCT application, WO 97/03959, discloses novel crystalline forms of atorvastatin calcium designated as Form I, Form II, and Form IV and method for their preparation. PCT application WO 97/03960 describes a procedure for converting the crystalline form of atorvastatin to the amorphous form.

The process described in the above mentioned patent involves dissolving the crystalline atorvastatin (form-I) in a non hydroxylic solvent like tetrahydrofuran or mixtures of tetrahydrofuran and toluene, followed by removal of the

solvents under high temperature (about 90°C) and high vacuum (about 5mm). This process may not suitable on a large scale as the conditions used for drying may lead to degradation of the product.

PCT application WO 00/71116 claims a process for the preparation of amorphous atorvastatin calcium where the crystalline form is dissolved in a non-hydroxilic solvent is treated with a non-polar hydrocarbon anti-solvent followed by the removal of the solvent to result in the amorphous form.

SUMMARY OF THE INVENTION

It is desirable to have a process, which provides amorphous atorvastatin using a procedure, which can be readily scaled up to a commercial scale. The present invention describes a process, which is ideal for large scale production of amorphous atorvastatin calcium.

The present invention provides a process for the preparation of atorvastatin calcium in an amorphous form which comprises dissolving the heterogeneous mixture of atorvastatin in a non-hydroxylic solvent followed by the addition of a suitable non-hydroxylic solvent to precipitate the product which is then isolated. Alternatively, the solution of atorvastatin in a non-

hydroxylic solvent is added to a non-hydroxylic solvent to induce precipitation.

The product can be isolated by any method known in the art such as by filtration, centrifugation or decantation. Typically, this product is isolated by filtration when any of the solvents within the scope of the process are used.

Major advantages of the present invention compared to the prior art processes are:

i. Produces amorphous atorvastatin consistently.
ii. Avoids the necessity to remove solvents.
iii. Simpler and faster filtration.
iv. Easy to operate on large-scale.
v. Avoids the use of hydrocarbons.

The present invention thus provides a simple and novel process for the preparation of amorphous atorvastatin calcium and hydrates thereof. The starting material used in the instant invention comprises of a mixture of both amorphous and crystalline forms – henceforth referred to as heterogeneous mixture. The present invention comprises of:

(i) Dissolving the heterogeneous mixture of atorvastatin calcium in a non-hydroxylic solvent;

(ii) Adding a non-hydroxylic solvent to precipitate the material; and

(iii) Removing the solvent by filtration to afford amorphous atorvastatin calcium.

The non-hydroxylic solvent in step (i) is tetrahydrofuran.

The non-hydoxylic solvent used in step (ii) is diisopropyl ether.

The amorphous atorvastatin calcium is isolated by filtration.

Amorphous atorvastatin calcium prepared according to the process of the present invention may be characterized by its x-ray powder diffraction pattern (Figures 2) as shown in the accompanied drawings. X-ray powder diffraction patterns (Figures 2) show no peaks which are characteristic of a heterogeneous mixture of atorvastatin calcium (Figure 1 of the accompanied drawings) thus demonstrating the amorphous nature of the product.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is the diffractogram of heterogeneous mixture of atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 2 is the diffractogram of amorphous atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

The present invention is illustrated by the following examples, which an intended to limit the effective scope of the claims.

DETAILED DESCRIPTION OF THE INVENTION

Example 1

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Amorphous Atorvasatin calcium).

A heterogeneous mixture of Atorvastatin calcium (10 g) was dissolved in tetrahydrofuran (200 ml) at 55°C and filtered over hyflo supercell. The filtrate was evaporated to 40 ml stage under vacuum and precipitated using diisopropyl ether (200 ml) at room temperature. The mixture was stirred for 30 min. at room temperature and filtered. The product was washed with diisopropyl ether (15 ml). The product was dried in vacuum tray drier (650 mm/Hg) at 55°C for 24 hrs to yield 9 g.

X-ray powder diffraction pattern (Figure 2 as shown in the accompanied drawings) demonstrates the amorphous nature of the product as against the heterogeneous nature of the starting material (Figure 1 as shown in the accompanied drawings)

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

WE CLAIM:

1. A process for the preparation of amorphous atorvastatin calcium and hydrates thereof which comprises:

(i) dissolving heterogeneous mixture of atorvastatin calcium in a non-hydroxylic solvent;

(ii) adding a non-hydroxylic solvent or adding the dissolved atorvastatin to the non-hydroxylic solvent to precipitate out atorvastatin calcium; and

(iii) removing the solvent by filtration followed by drying to afford amorphous atorvastatin calcium.

2. The process as claimed in claim 1, wherein the non-hydroxylic solvent in step (i) is tetrahydrofuran.

3. The process as claimed in claim 1, wherein the non-hydoxylic solvent used in step (ii) is diisopropyl ether.

4. The process as claimed in claim 1, wherein said amorphous atorvastatin calcium is isolated by filtration.

5. The process as claimed in claim 1 wherein said heterogenous mixture of atorvastatin calcium comprises a mixture of both amorphous and crystalline forms.

Figure 1

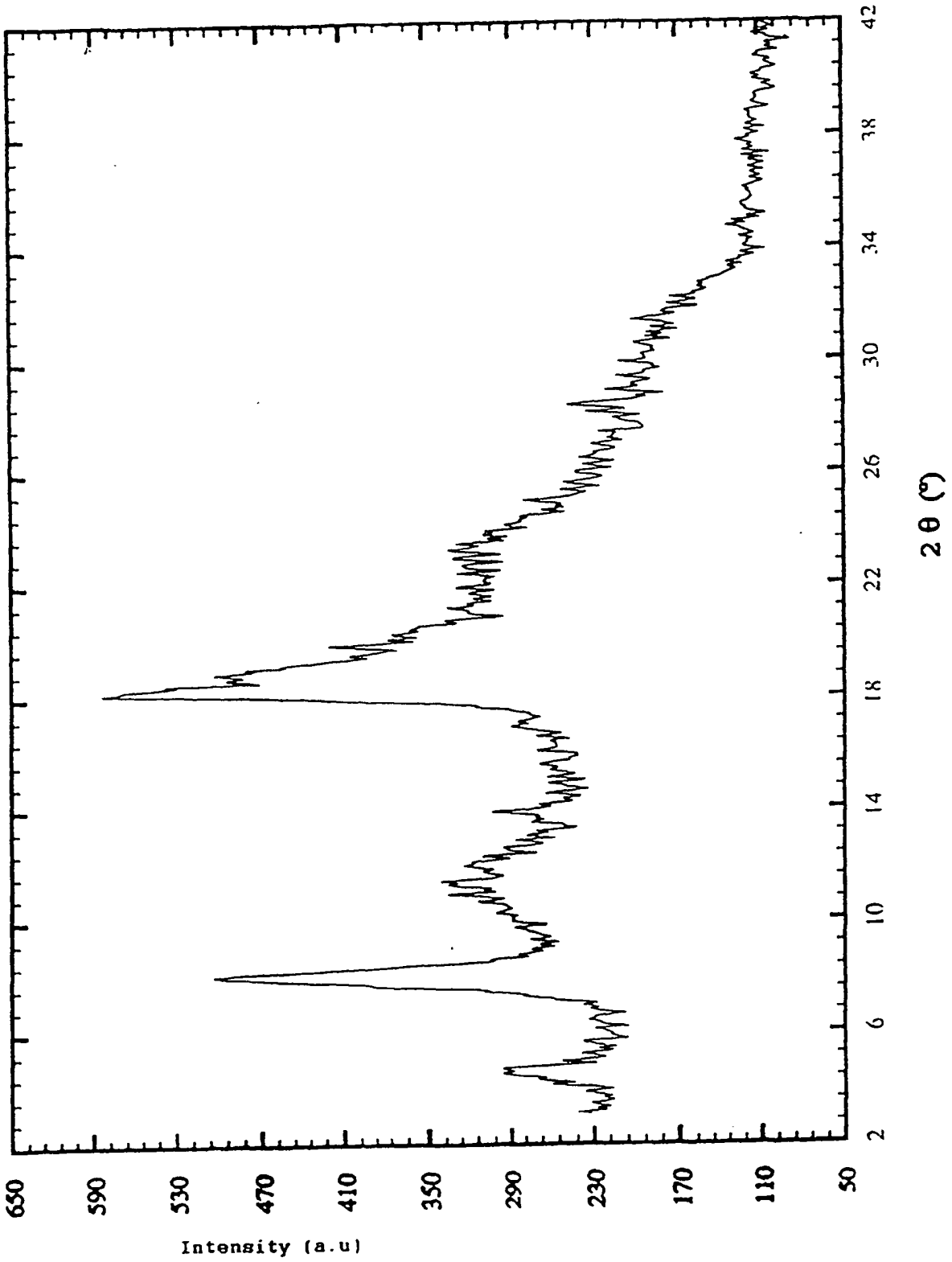
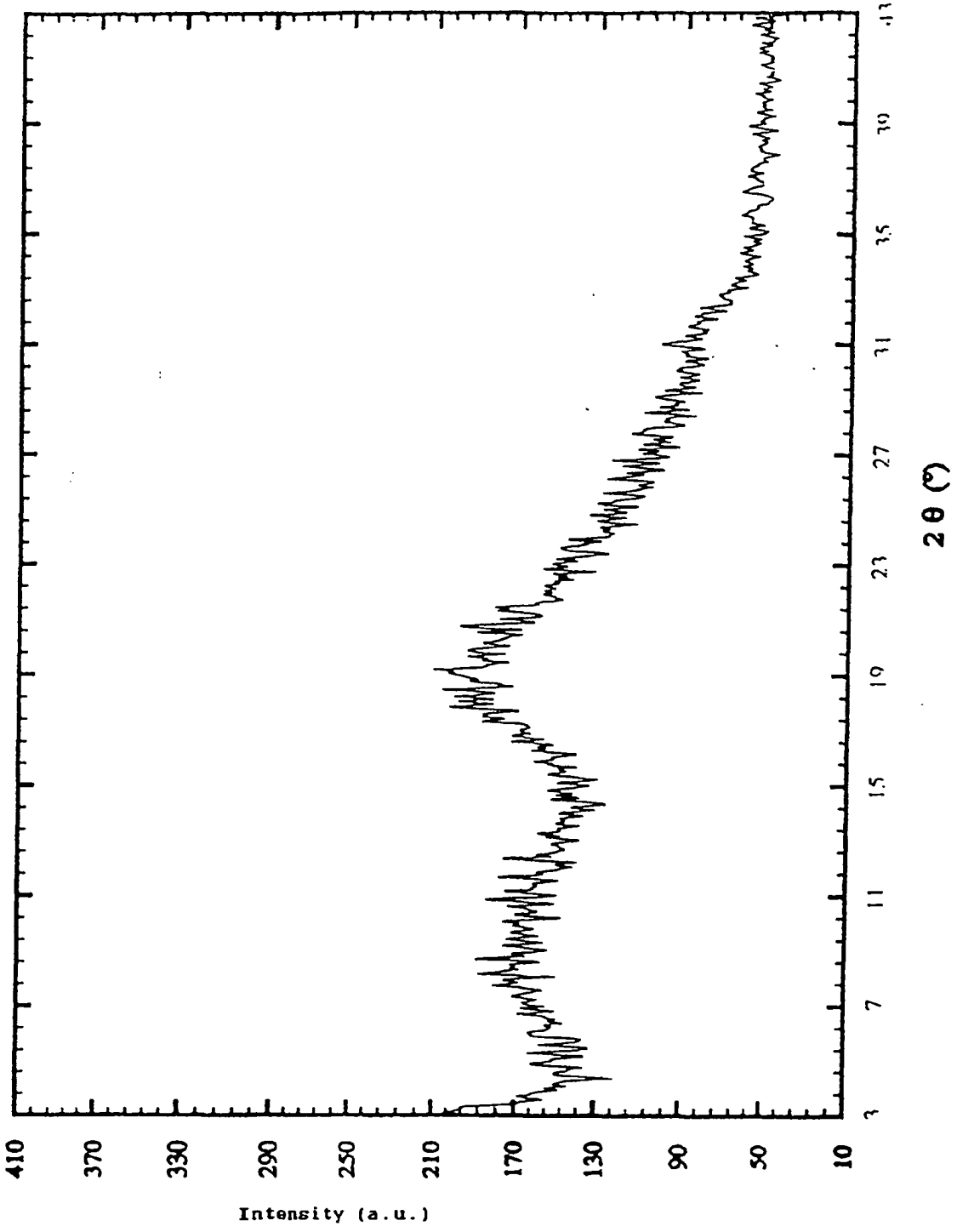

650
590
530
470
410
350
290
230
170
110
50
Intensity (a.u)
2
6
10
14
18
22
26
30
34
38
42
2 θ (°)

Figure 2


410
370
330
290
250
210
170
130
90
50
10
Intensity (a.u.)
3
7
11
15
19
23
27
31
35
39
2θ (°)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 01/00004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 A61K31/40 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 385 929 A (BJORGE SUSAN M ET AL) 31 January 1995 (1995-01-31) example 2	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2001	25/09/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 01/00004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 01/00004

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